Original Investigation

Association Between Sitagliptin Use and Heart Failure Hospitalization and Related Outcomes in Type 2 Diabetes Mellitus

Secondary Analysis of a Randomized Clinical Trial

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IMPORTANCE Previous trial results have suggested that dipeptidyl peptidase 4 inhibitor (DPP4i) use might increase heart failure (HF) risk in type 2 diabetes mellitus (T2DM). The DPP4i sitagliptin has been shown to be noninferior to placebo with regard to primary and secondary composite atherosclerotic cardiovascular (CV) outcomes in the Trial Evaluating Cardiovascular Outcomes With Sitagliptin (TECOS).

OBJECTIVE To assess the association of sitagliptin use with hospitalization for HF (hHF) and related outcomes.

DESIGN, SETTING, AND PARTICIPANTS TECOS was a randomized, double-blind, placebo-controlled study evaluating the CV safety of sitagliptin vs placebo, each added to usual antihyperglycemic therapy and CV care among patients with T2DM and prevalent atherosclerotic vascular disease. The median follow-up was 2.9 years. The setting was 673 sites in 38 countries. Participants included 14 671 patients with T2DM and atherosclerotic vascular disease. The study dates were December 2008 through March 2015.

INTERVENTIONS Patients were randomized to sitagliptin vs placebo added to standard care.

MAIN OUTCOMES AND MEASURES Prespecified secondary analyses compared the effect on hHF, hHF or CV death, and hHF or all-cause death composite outcomes overall and in prespecified subgroups. Supportive analyses included total hHF events (first plus recurrent) and post-hHF death. Meta-analyses evaluated DPP4i effects on hHF and on hHF or CV death.

RESULTS Of 14 671 patients, 7332 were randomized to sitagliptin and 7339 to placebo. Hospitalization for HF occurred in 3.1% (n = 228) and 3.1% (n = 229) of the sitagliptin and placebo groups, respectively (unadjusted hazard ratio, 1.00; 95% CI, 0.83-1.19). There was also no difference in total hHF events between the sitagliptin (n = 345) and placebo (n = 347) groups (unadjusted hazard ratio, 1.00; 95% CI, 0.80-1.25). Post-hHF all-cause death was similar in the sitagliptin and placebo groups (29.8% vs 28.8%, respectively), as was CV death (22.4% vs 23.1%, respectively). No heterogeneity for the effect of sitagliptin on hHF was observed in subgroup analyses across 21 factors ($P > .10$ for all interactions). Meta-analysis of the hHF results from the 3 reported DPP4i CV outcomes trials revealed moderate heterogeneity ($I^2 = 44.9$, $P = .16$).

CONCLUSIONS AND RELEVANCE Sitagliptin use does not affect the risk for hHF in T2DM, both overall and among high-risk patient subgroups.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT00790205

JAMA Cardiol. 2016;1(2):126-135. doi:10.1001/jamacardio.2016.0103
Published online April 13, 2016.

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Type 2 diabetes mellitus (T2DM) is associated with multiple cardiovascular (CV) complications, possibly exacerbated by certain antihyperglycemic therapies. Because of these latter concerns, US and European regulatory guidance calls for rigorous CV safety assessment of all antihyperglycemic medications developed for T2DM.[1] While the focus of such CV safety assessment has been on the composite outcomes of CV death, acute coronary syndromes, and stroke, heart failure (HF) has emerged as an increasingly important consideration.[2] The diagnosis of HF is a risk factor for T2DM,[3] and T2DM is associated with an approximate 30% increased risk of hospitalization for HF (hHF) in contemporary cohorts, with worse prognosis of patients with HF to a similar extent.[4] Moreover, the use of some antihyperglycemic medications has been associated with new or worsening HF, such as the thiazolidinediones,[5,6] as well as dual peroxisome proliferator-activated receptor α and γ agonists.[7,8]

More recently, dipeptidyl peptidase 4 inhibitor (DPP4i) use has been associated with increased hHF risk, with ongoing uncertainty regarding the validity of the findings and their clinical implications.[9] Specifically, saxagliptin use was associated with a significant increase in hHF risk in the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients With Diabetes Mellitus-Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI 53) trial.[10] Alogliptin use was also associated with a numerically higher but not statistically significant increased risk for hHF in the Examination of Cardiovascular Outcomes With Alogliptin vs Standard of Care (EXAMINE) trial.[11] Meta-analyses[12,13] of these and other DPP4i investigations suggest that these agents may be associated with up to a 25% increased risk for hHF.

The Trial Evaluating Cardiovascular Outcomes With Sitagliptin (TECOS) is the third completed DPP4i, large-scale, randomized CV outcomes trial. Overall, TECOS results demonstrated that sitagliptin was noninferior to placebo with regard to its primary and secondary composite CV outcomes.[14] This report explores in-depth potential associations of sitagliptin use with hHF and associated CV clinical outcomes, either overall or in key patient subgroups according to a prespecified analysis plan. The additive TECOS evidence with respect to DPP4i effects on hHF risk is also used to place these findings into a new overall context.

Key Points

Question What is the effect of sitagliptin use on risk for hospitalization for heart failure and related outcomes?

Findings This randomized, placebo-controlled clinical trial included 14 671 adults with type 2 diabetes mellitus and prevalent atherosclerotic vascular disease. In secondary analyses, over a median follow-up of 2.9 years, there were no significant differences between sitagliptin vs placebo for the risk of hospitalization for heart failure (3.1% vs 3.1%, respectively) or for the composite of hospitalization for heart failure or cardiovascular death (7.3% vs 7.2%, respectively).

Meaning Sitagliptin use has a neutral effect on hospitalization for heart failure risk in patients with type 2 diabetes mellitus at high cardiovascular risk.

Methods

Study Design, Population, and Oversight

The design, protocol, Consolidated Standards of Reporting Trials diagram, and primary results of TECOS have been previously published.[14,15] The present study is a prespecified secondary analysis of TECOS, which was a randomized, double-blind, event-driven study evaluating the CV safety of sitagliptin vs placebo, each added to usual antihyperglycemic therapy and CV care among patients with T2DM and prevalent atherosclerotic vascular disease. TECOS was designed and conducted by the Duke Clinical Research Institute and the University of Oxford Diabetes Trials Unit in an academically independent collaboration with the sponsor (Merck Sharp & Dohme Corp). The database was located at and independently verified by the Duke Clinical Research Institute. The protocol[14] was approved by the ethics committees associated with all participating trial sites, and all participants provided written informed consent for trial participation.

Study Population

Eligible patients had T2DM and prevalent coronary, cerebrovascular, or peripheral atherosclerotic vascular disease; were 50 years or older; and had a baseline glycated hemoglobin (A_{1c}) level of 6.5% to 8.0% on stable antihyperglycemic medication. Trial exclusions included the use of a DPP4i, glucagon-like peptide 1 receptor agonists (GLP-1 RAs), or rosiglitazone during the preceding 3 months; 2 or more episodes of hypoglycemia requiring third-party assistance in the previous 12 months; or an estimated glomerular filtration rate less than 30 mL/min/1.73 m^2 at baseline. Patients with previous HF were not excluded.

Randomization and Study Medication

Participants were randomly assigned 1:1 to treatment with 100 mg daily of sitagliptin (50 mg daily if the baseline estimated glomerular filtration rate was between 30 and <50 mL/min/1.73 m^2) or matching placebo, with predefined dosage adjustments throughout the trial based on changes in the estimated glomerular filtration rate.[15] The A_{1c} level was measured locally at enrollment, at 4 and 8 months, and then annually. Open-label addition or titration of antihyperglycemic medications, other than a DPP4i or GLP-1 RA, was encouraged throughout the trial, targeting A_{1c} levels in accord with regional standards of care and individualized goals.

Outcomes

Prespecified HF-related outcomes included the time to the first hHF, the time to the first event of hHF or CV death, the time to the first event of hHF or all-cause death, total hHF events (including recurrent hHF), and the time to the first hHF in subgroup analyses by 21 factors of interest, of which 16 were prespecified in the main trial statistical analysis plan and 5 were added post hoc (eAppendix 1 in the Supplement). Among patients with hHF, post-hHF death was also summarized by

treatment group and was defined as deaths occurring either during the index hHF or at any time thereafter, with CV death and all-cause death reported. An independent clinical events committee masked to treatment allocation adjudicated all events of hHF and death using end point definitions as previously reported,[15] derived from definitions of the Standardized Data Collection for Cardiovascular Trials Initiative working group (http://www.clinpage.com/images/uploads/endpoint-defs_11-16-2010.pdf). The hHF outcome was defined as at least 12-hour inpatient or emergency department care for HF, with clinical manifestation of HF that included at least 1 of the following: new or worsening dyspnea, orthopnea, paroxysmal nocturnal dyspnea, edema, pulmonary basilar crackles, jugular venous distension, or radiological evidence of worsening HF, together with additional or increased therapy, including intravenous treatment with diuretic, inotrope, or vasodilator therapy, or the use of a mechanical or surgical intervention (mechanical circulatory support, heart transplantation, or ventricular pacing to improve cardiac function) or the use of ultrafiltration, hemofiltration, or dialysis specifically directed at treatment of HF (see the clinical events committee definitions and process in eAppendix 2 in the Supplement).

Statistical Analysis

Baseline characteristics for the randomized population were summarized using the mean ±1 SD or the median and interquartile range for quantitative data and as proportions for categorical data. The time to the first occurrence of hHF was a prespecified secondary analysis in the original TECOS protocol and statistical analysis plan.[15] In response to the hHF signals reported by the SAVOR-TIMI 53 and EXAMINE DPP4i trials during the conduct of TECOS, additional exploratory hHF analyses were planned prospectively and before trial completion and unmasking in a supplementary HF statistical analysis plan (eAppendix 1 in the Supplement) to further investigate the potential effect of sitagliptin use on hHF-related outcomes.

As per the original trial statistical analysis plan,[14] the time to the first occurrence of hHF was evaluated using a Cox proportional hazards regression model that included treatment and history of HF as explanatory factors, with region as a stratification factor, when analyzing the intent-to-treat population. Analyses added in the supplemental HF statistical analysis plan included similar methods for analysis of the time to the composite of the first hHF or CV death or hHF or all-cause death, unadjusted analysis of the time to the first hHF and the hHF or CV death composite, and subgroup analyses of hHF by key prespecified baseline characteristics, including prevalent HF at baseline. Exposure times of all patients were censored at the date they were last known to be free of all components of the individual and composite outcomes analyzed. The method by Andersen and Gill[16] was used to analyze all first plus recurrent hHF events. Interaction terms in the Cox proportional hazards regression models were used to assess heterogeneity of the effect of sitagliptin vs placebo on the risk of hHF outcomes among each subgroup analyzed. All analyses were performed by Duke Clinical Research Institute statisticians (M.J.P., J.G., and Y.L.) independent of the sponsor using a software program (SAS, version 9.4; SAS Institute Inc). Meta-analyses using random-effects models on summative data were performed for hHF outcomes and the composite outcome of hHF or CV death without adjustment for baseline HF using data from SAVOR-TIMI 53, EXAMINE, and TECOS with a software program (Comprehensive Meta-Analysis Software, version 2.0; Biostat, Inc), with heterogeneity assessed among studies using the Cochran *Q* test and I^2 index.

Results

Study Patients

The study setting was 673 sites in 38 countries. Of 14 671 patients in the intent-to-treat population randomized between December 16, 2008, and July 31, 2012, a total of 7332 were assigned to sitagliptin and 7339 to placebo. Among the 2643 patients (18.0%) with previous HF at trial entry, 1303 were assigned to sitagliptin and 1340 to placebo. During a median follow-up surveillance for fatal plus nonfatal outcomes of 2.9 years (interquartile range, 1.4-5.7 years), 95.1% of sitagliptin-assigned and 94.1% of placebo-assigned patients completed the study, with 26.1% and 27.5%, respectively, discontinuing study medication prematurely. End-of-study vital status was obtained on 97.5% of patients. Overall, 457 patients (3.1%) had at least 1 hHF event, with baseline characteristics stratified by those with vs without hHF events listed in **Table 1**. Baseline data for the subset of patients with previous HF, stratified by randomized treatment assignment, are listed in eTable 1 in the Supplement. There was no difference between the randomized treatment groups in blood pressure, heart rate, or weight throughout the trial (eFigure 1 in the Supplement).

HF-Related Outcomes

The HF-related outcomes by randomized treatment group are summarized in **Table 2** and **Figure 1**. The rate of a first hHF did not differ between the groups, occurring in 228 patients (3.1%) in the sitagliptin group and 229 patients (3.1%) in the placebo group, with an unadjusted hazard ratio (HR) of 1.00 (95% CI, 0.83-1.19) (Table 2 and Figure 1A). The HR was unchanged with adjustment for region of enrollment and baseline HF (HR, 1.00; 95% CI, 0.83-1.20) and in fully adjusted analyses (HR, 1.02; 95% CI, 0.83-1.26). There was also no difference between sitagliptin vs placebo for the composite outcomes of hHF or CV death (538 vs 525 events; HR, 1.02, 95% CI, 0.90-1.14) (Figure 1B) or hHF or all-cause death (685 vs 682 events; HR, 1.00; 95% CI, 0.90-1.11) (Figure 1C).

The numbers of patients with multiple hHF events were similar between the sitagliptin and placebo groups (63 vs 69, respectively) (Table 2). The cumulative number of hHF events (first plus recurrent) was not different between the groups (345 vs 347, respectively; HR, 1.00; 95% CI, 0.80-1.25). There was no evidence for heterogeneity of randomized treatment effect by the time to hHF, with a nonsignificant treatment × time interaction (P = .51). Among the subset of patients with previous HF at baseline, there were no significant differences observed between the treatment groups in hHF, CV death, or the composite of the 2.

Table 1. Baseline Characteristics of Patients in the TECOS Intent-to-Treat Population, Stratified by Those With vs Without First Hospitalization for Heart Failure During the Trial

Variable	With (n = 457)	Without (n = 14 214)
Age, mean (SD), y	68.5 (7.6)	65.4 (8.0)
Female sex, %	25.2	29.4
Race/ethnicity, %		
White	76.6	67.6
Black	6.8	2.9
Asian	11.4	22.6
Other	5.3	6.9
Not Hispanic or Latino	91.5	87.6
Hispanic or Latino	8.5	12.4
Region, %		
North America	28.7	17.3
Latin America	5.9	10.2
Western Europe	13.8	14.2
Eastern Europe	26.3	27.1
Asia Pacific or other	25.4	31.3
Diabetes duration, mean (SD), y	12.3 (8.7)	11.6 (8.1)
Glycated hemoglobin, mean (SD), %	7.3 (0.5)	7.2 (0.5)
Glycated hemoglobin category, %		
<7%	35.2	33.9
≥7 to <7.5%	27.1	30.8
≥7.5%	37.6	35.2
eGFR, mean (SD), mL/min/1.73 m^2	66.5 (20.9)	75.2 (21.1)
Prior vascular disease, %		
Coronary artery disease	85.3	73.7
Myocardial infarction	58.2	42.1
Cerebrovascular	29.1	24.3
Peripheral artery	17.3	16.6
Prior heart failure, %	41.8	17.3
Baseline heart failure severity among those with prior heart failure, %		
NYHA class I	18.8	20.4
NYHA class II	39.3	50.4
NYHA class III	16.8	13.4
NYHA class IV	1.6	0.4
NYHA class not reported	23.6	15.4
Blood pressure, mean (SD), mm Hg		
Systolic	134.0 (19.4)	135.1 (16.9)
Diastolic	74.4 (11.2)	77.3 (10.4)
Weight, mean (SD), kg	89.6 (20.4)	84.9 (18.9)
Body mass index, mean (SD)[a]	31.4 (6.3)	30.2 (5.6)
Cigarette smoking, %		
Current	11.4	11.4
Former	47.9	39.6
Never	40.7	49.0
Antihyperglycemic therapies, %		
Metformin	72.2	81.9
Sulfonylurea	46.2	45.3
Thiazolidinedione	2.8	2.7
Insulin	32.4	22.9
Cardiovascular medications, %		
Statin	83.6	79.8
Aspirin	74.6	78.6
Nonaspirin antiplatelet agent	21.7	21.7
ACE inhibitor or angiotensin receptor blocker	85.6	78.5
β-Blocker	71.8	63.3
Diuretic	69.1	40.1
Calcium channel blocker	39.2	33.6

Abbreviations: ACE, angiotensin-converting enzyme; eGFR, estimated glomerular filtration rate; NYHA, New York Heart Association; TECOS, Trial Evaluating Cardiovascular Outcomes With Sitagliptin.

[a] Calculated as weight in kilograms divided by height in meters squared.

Death during or after hHF did not differ by randomized group (Table 2), with CV death occurring in 51 of 228 sitagliptin patients (22.4%) and 53 of 229 placebo patients (23.1%). All-cause death occurred in 68 of 228 sitagliptin patients (29.8%) and 66 of 229 placebo patients (28.8%).

As shown in **Figure 2**, the rate of hHF varied substantially across subgroups defined by baseline characteristics but with no heterogeneity of effect for sitagliptin vs placebo on hHF ($P > .10$ for all interactions). Similar data for subgroup analyses by randomized assignment for the composite outcome of hHF or CV death are shown in eFigure 2 in the Supplement, likewise with no evidence of heterogeneity of effect ($P > .05$ for all interactions).

For comparison across the 3 reported DPP4i CV outcomes trials, baseline characteristics of the SAVOR-TIMI 53, EXAMINE, and TECOS study populations are listed in eTable 2 in the Supplement, demonstrating substantial similarity. The pooled estimate for the effect of a DPP4i vs placebo on hHF in these 3 large CV outcomes trials (**Figure 3**A) showed a numerically increased HR of 1.14 (95% CI, 0.97-1.34), with moderate heterogeneity ($P = .16$, $I^2 = 44.9$). The pooled estimate for the hHF or CV death composite (Figure 3B) showed no significant difference between the DPP4i and placebo groups (HR, 1.06; 95% CI, 0.98-1.15), with minimal heterogeneity ($P = .36$, $I^2 = 1.29$).

Discussion

In patients with T2DM and prevalent atherosclerotic vascular disease participating in the TECOS global, randomized CV outcomes trial, sitagliptin compared with placebo did not affect the risk for hHF or for the composite hHF or CV death or hHF or all-cause death outcomes. There was also no increased risk of HF observed in any subgroup analyzed, including those at highest risk for hHF, such as patients with previous HF, kidney dysfunction, concomitant insulin use, and highest A_{1c} level, as well as the elderly.

Table 2. Heart Failure–Related Outcomes for Sitagliptin vs Placebo in the TECOS Intent-to-Treat Population and in the Subset of Patients With Prior Heart Failure at Baseline

Variable	No./Total No. (%)		HR (95% CI)	*P* Value
	Sitagliptin (n = 7332)	Placebo (n = 7339)		
Overall Intent-to-Treat Population				
First hospitalization for heart failure (unadjusted)	228 (3.1)	229 (3.1)	1.00 (0.83-1.19)	.95
Adjusted for region and prior heart failure at baseline	NA	NA	1.00 (0.83-1.20)	.98
Multivariable adjusted[a]	NA	NA	1.02 (0.83-1.26)	.82
Composite of hospitalization for heart failure or cardiovascular death (unadjusted)	538 (7.3)	525 (7.2)	1.02 (0.90-1.14)	.81
Adjusted for region and prior heart failure at baseline	NA	NA	1.02 (0.90-1.15)	.74
Composite of hospitalization for heart failure or all-cause death (unadjusted)	685 (9.3)	682 (9.3)	1.00 (0.90-1.11)	.93
Total hospitalization for heart failure events (first plus recurrent) (unadjusted)[b]	345	347	1.00 (0.80-1.25)	>.99
Patients with 2 events	37	44	NA	NA
Patients with ≥3 events	26	25	NA	NA
Death during or after first hospitalization for heart failure (unadjusted)				
Cardiovascular death	51/228 (22.4)	53/229 (23.1)	NA	NA
All-cause death	68/228 (29.8)	66/229 (28.8)	NA	NA
Subset of Patients With Prior Heart Failure at Baseline				
First hospitalization for heart failure (unadjusted)	97/1303 (7.4)	94/1340 (7.0)	1.03 (0.77-1.36)	.86
Cardiovascular death (unadjusted)	120/1303 (9.2)	133/1340 (9.9)	0.91 (0.71-1.17)	.46
Composite of hospitalization for heart failure or cardiovascular death (unadjusted)	183/1303 (14.0)	191/1340 (14.3)	0.96 (0.79-1.18)	.71
All-cause death	166/1303 (12.7)	182/1340 (13.6)	0.92 (0.75-1.14)	.46

Abbreviations: eGFR, estimated glomerular filtration rate; HR, hazard ratio; NA, not applicable; TECOS, Trial Evaluating Cardiovascular Outcomes With Sitagliptin.

[a] Adjusted for ethnicity, race, prior myocardial infarction, coronary stenosis exceeding 50%, prior coronary artery bypass graft surgery, prior peripheral arterial disease, prior heart failure, cigarette smoking, diuretic use, age, body mass index, systolic blood pressure, diastolic blood pressure, eGFR, glycated hemoglobin, high-density lipoprotein cholesterol, and triglycerides and stratified by region.

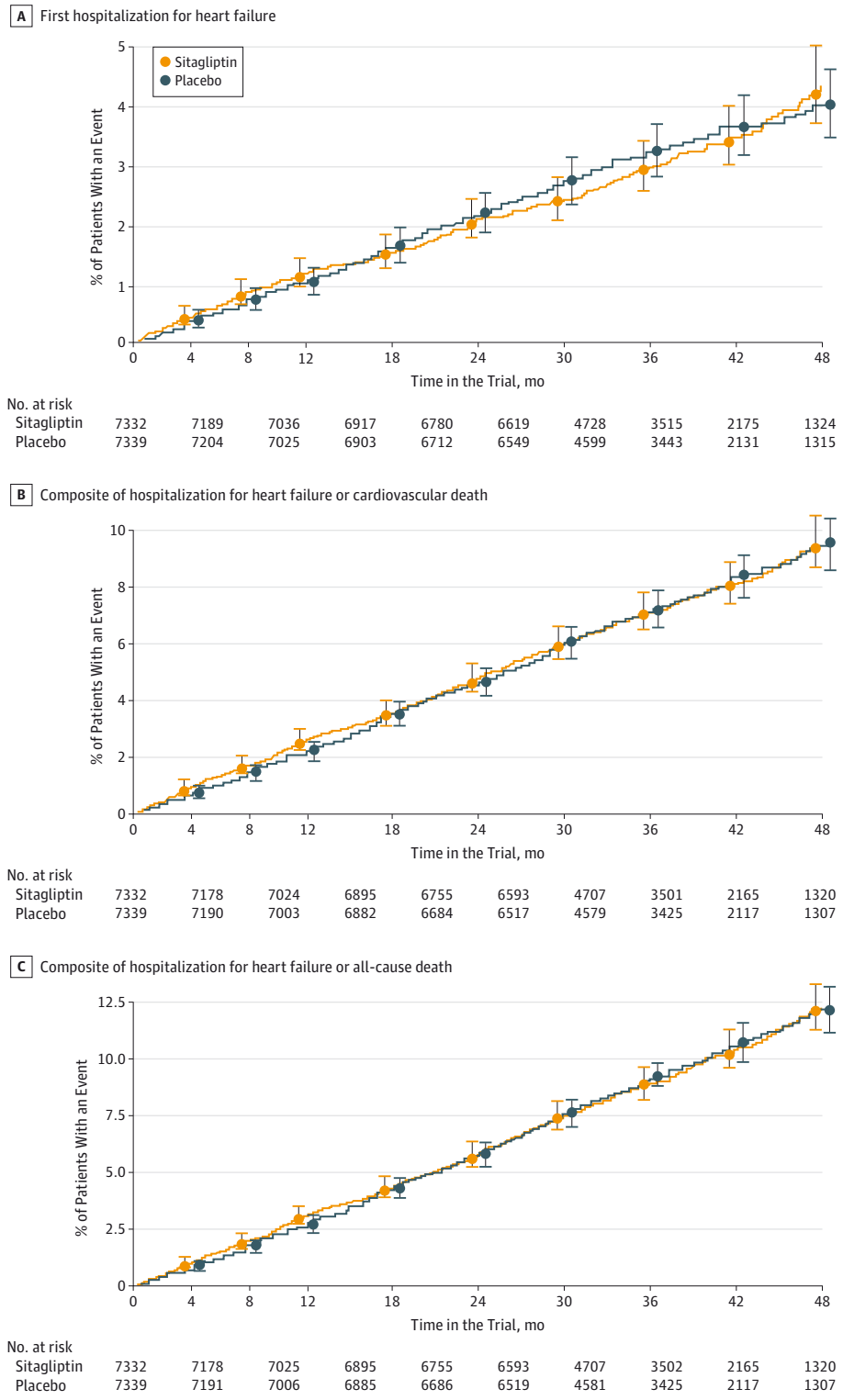
[b] Analyzed using the method of Andersen and Gill.[16]

The TECOS findings do not confirm the signals for increased risk of hHF observed in 2 previous large DPP4i trials. The SAVOR-TIMI 53 trial[10] assessed the effects of saxagliptin vs placebo on hHF in patients with T2DM, and a history or risk of CV events showed an unexpected 27% increased risk for hHF (HR, 1.27; 95% CI, 1.07-1.51) associated with saxagliptin use. The EXAMINE trial[11] of alogliptin vs placebo in patients with T2DM and a recent acute coronary syndrome event showed a nonsignificant numerical increase of hHF associated with alogliptin use (HR, 1.19; 95% CI, 0.90-1.58). Previous meta-analyses[12,13] of DPP4i agents, including saxagliptin, alogliptin, linagliptin, vildagliptin, and sitagliptin, have shown statistically significant increased pooled estimates of DPP4i-associated risks for hHF of 24% to 25%. In contrast, meta-analysis herein limited to the TECOS findings and those from the SAVOR-TIMI 53 and EXAMINE trials showed a nonsignificant 14% increase. This meta-analysis is not intended to be a comprehensive systematic review of all DPP4i effects on hHF. Rather, the objectives are to capitalize on the commonality of these trial designs (using placebo controls and targeting glycemic equipoise between the groups) and the similarities of the patient populations enrolled (with prospective capture and central adjudication of hHF events using virtually identical processes and outcome definitions) and to place the present results into the context of a similar meta-analysis[10] of the SAVOR-TIMI 53 and EXAMINE trial outcomes previously published. Given the moderate heterogeneity in this analysis, important differences across the DPP4i class cannot be excluded.

It is unclear why unexpected signals for increased hHF risk were seen with saxagliptin, as well as a similar adverse trend observed with alogliptin, compared with the neutral effect of sitagliptin in TECOS. Differences in the trial populations are unlikely to explain the discordant hHF outcomes. The TECOS population had well-managed CV and glycemic risk factors at entry and was broadly similar to those studied in the EXAMINE and SAVOR-TIMI 53 trials with regard to baseline characteristics and the use of background antihyperglycemic and CV medications (eTable 2 in the Supplement).[14,17-19] The annualized hHF rates observed across these trials were low and comparable (1.1%, 1.3%, and 2.3% in TECOS, SAVOR-TIMI 53, and EXAMINE, respectively). TECOS and SAVOR-TIMI 53 both enrolled patients with previous atherosclerotic vascular disease, although 21% (n = 3533) of the trial cohort in SAVOR-TIMI 53 had multiple CV risk factors only. The EXAMINE trial enrolled patients at higher CV risk after recent acute coronary syndrome events, as evidenced by their numerically higher annualized hHF. Previous CV disease was an independent predictor for hHF in the SAVOR-TIMI 53 trial,[10] but no heterogeneity was seen for the effect of saxagliptin on hHF risk when analyses were stratified by prevalent CV disease.

In TECOS, 2643 patients (18.0%) had prior HF compared with 2105 patients (12.8%) in the SAVOR-TIMI 53 trial and 1533 patients (28.9%) in the EXAMINE trial. In all 3 trials, patients

Figure 1. Kaplan-Meier Plots

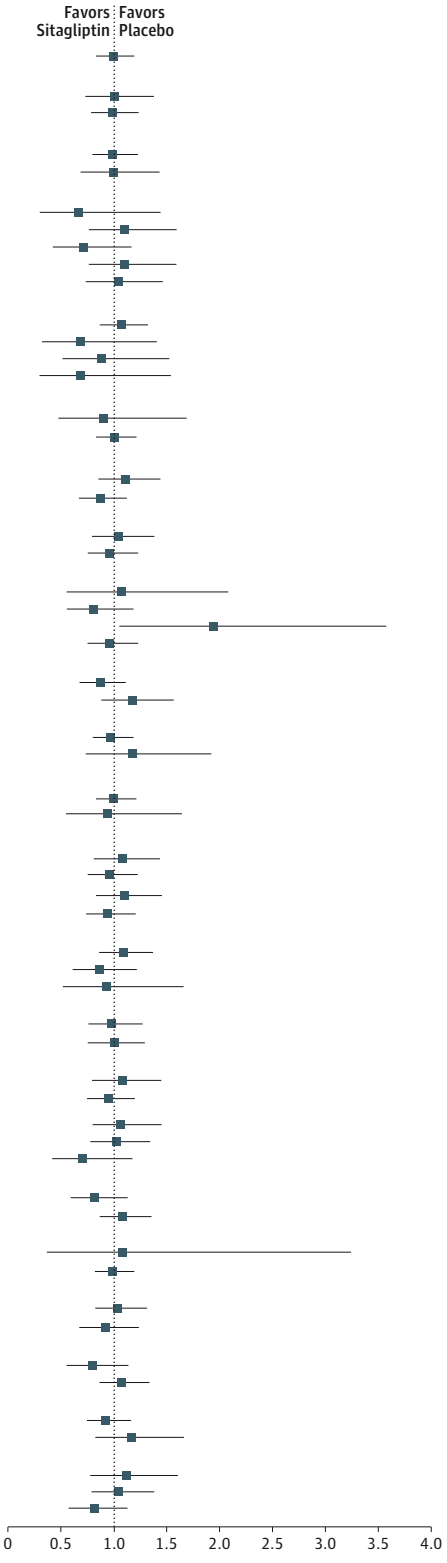


Treatment with sitagliptin is compared with placebo.

with prior HF were at increased risk for hHF but with no evidence for heterogeneity of the DPP4i effect by prior HF in any of the trials,[10,11] making it unlikely that different proportions of patients with prior HF across the 3 trials account for the discordant hHF findings. The SAVOR-TIMI 53 and EXAMINE trials allowed higher A_{1c} levels at trial entry (up to 12% and 11%, respectively) in contrast to the TECOS upper limit of 8%. However, in both TECOS and SAVOR-TIMI 53, there was no asso-

Figure 2. Stratified Analyses for Sitagliptin vs Placebo on First Hospitalization for Heart Failure for Prespecified and Post Hoc or Exploratory Subgroups

Subgroup	Sitagliptin No./Total No.	Placebo No./Total No.	HR (95% CI)	P Value for Interaction
Overall	228/7332	229/7339	1.00 (0.83-1.20)	
Age				
≤Median	76/3676	74/3640	1.00 (0.73-1.38)	.92
>Median	148/3498	153/3537	0.98 (0.79-1.23)	
Sex[a]				
Male	171/5198	171/5176	0.99 (0.80-1.23)	.99
Female	57/2134	58/2163	0.99 (0.69-1.43)	
Region				
Latin American	11/744	16/727	0.67 (0.31-1.44)	.48
Asia Pacific and other	62/2313	54/2252	1.11 (0.77-1.59)	
Western Europe	27/1051	36/1025	0.71 (0.43-1.17)	
Eastern Europe	63/1980	57/1985	1.11 (0.77-1.58)	
North America	65/1244	66/1350	1.04 (0.74-1.47)	
Race[a]				
White	181/4955	169/5002	1.07 (0.87-1.33)	.47
Black	12/206	19/241	0.68 (0.33-1.41)	
Asian	25/1654	27/1611	0.89 (0.52-1.53)	
Other	10/517	14/485	0.68 (0.30-1.54)	
Ethnicity[a]				
Hispanic or Latino	18/886	21/912	0.90 (0.48-1.69)	.75
Not Hispanic or Latino	210/6446	208/6427	1.00 (0.83-1.21)	
Diabetes duration[a]				
≤Median	119/3813	108/3895	1.11 (0.86-1.44)	.19
>Median	107/3514	121/3437	0.87 (0.67-1.13)	
Prior congestive heart failure				
Yes	97/1303	94/1340	1.05 (0.79-1.39)	.67
No	131/6029	135/5999	0.96 (0.76-1.23)	
Baseline heart failure severity				
NYHA class I	20/285	16/250	1.08 (0.56-2.09)	.12
NYHA class ≥II	48/809	62/876	0.82 (0.56-1.19)	
NYHA class not reported	29/209	16/214	1.94 (1.05-3.57)	
None	131/6029	135/5999	0.96 (0.76-1.23)	
Prior myocardial infarction				
Yes	125/3133	141/3122	0.87 (0.69-1.11)	.12
No	103/4199	88/4217	1.18 (0.89-1.57)	
Prior coronary artery disease				
Yes	191/5397	199/5466	0.97 (0.79-1.18)	.45
No	37/1935	30/1873	1.19 (0.73-1.92)	
Prior hypertension[a]				
Yes	204/6344	203/6304	1.00 (0.82-1.21)	.85
No	24/988	26/1035	0.94 (0.54-1.64)	
Body mass index[a]				
≤Median	99/3668	90/3597	1.08 (0.81-1.43)	.55
>Median	126/3596	133/3673	0.96 (0.75-1.23)	
<30	107/3907	95/3828	1.10 (0.84-1.45)	.40
≥30	118/3357	128/3442	0.94 (0.73-1.21)	
Systolic blood pressure, mm Hg				
<140	143/4386	133/4429	1.08 (0.86-1.37)	.54
≥140 to <160	63/2283	71/2228	0.86 (0.62-1.21)	
≥160	22/640	24/663	0.93 (0.52-1.65)	
Glycated hemoglobin				
≤Median	117/3776	119/3830	0.98 (0.76-1.27)	.95
>Median	110/3549	110/3501	1.00 (0.76-1.30)	
Renal function				
<60 eGFR, mL/min/1.73 m^2	91/1667	84/1657	1.07 (0.80-1.44)	.52
≥60 eGFR, mL/min/1.73 m^2	134/5587	142/5617	0.95 (0.75-1.20)	
≥30 to ≤60 eGFR, mL/min/1.73 m^2 [a]	91/1666	84/1655	1.07 (0.80-1.44)	.36
≥60 to <90 eGFR, mL/min/1.73 m^2 [a]	109/3943	105/3936	1.02 (0.78-1.34)	
≥90 eGFR, mL/min/1.73 m^2 [a]	25/1644	37/1681	0.70 (0.42-1.17)	
Insulin				
Yes	68/1724	80/1684	0.82 (0.59-1.13)	.16
No	160/5608	149/5655	1.08 (0.87-1.35)	
Thiazolidinedione				
Yes	7/196	6/200	1.09 (0.37-3.24)	.87
No	221/7136	223/7139	0.99 (0.82-1.19)	
ACE inhibitor				
Yes	147/3932	141/3932	1.04 (0.82-1.31)	.53
No	81/3400	88/3407	0.92 (0.68-1.24)	
Angiotensin receptor blocker				
Yes	54/2052	70/2120	0.80 (0.56-1.14)	.16
No	174/5280	159/5219	1.08 (0.87-1.33)	
β-Blocker				
Yes	158/4647	170/4675	0.93 (0.75-1.16)	.27
No	70/2685	59/2664	1.17 (0.83-1.66)	
Diuretic				
Thiazide	60/1682	57/1782	1.12 (0.78-1.61)	.38
Other	104/1294	95/1262	1.05 (0.79-1.38)	
None	64/4356	77/4295	0.81 (0.58-1.13)	



Body mass index is calculated as weight in kilograms divided by height in meters squared. ACE indicates angiotensin-converting enzyme; eGFR, estimated glomerular filtration rate; HR, hazard ratio; and NYHA, New York Heart Association.

[a] Post hoc subgroups.

ciation between baseline A_{1c} level and hHF risk, nor was there heterogeneity of the effect of study drug on hHF events by baseline A_{1c} level in either trial.

Differences in trial duration might influence detection of a risk signal for hHF, with TECOS having the longest duration of the DPP4i trials reported to date. The median follow-up periods for death were 3.0 years in TECOS, 1.9 years in SAVOR-TIMI 53, and 1.5 years in EXAMINE. In this regard, it is notable that in the SAVOR-TIMI 53 trial the greatest incremental risk for hHF was observed early in the trial. Saxagliptin vs placebo showed hHF HRs of 1.80 (95% CI, 1.29-2.55) at 6 months and 1.46 (95% CI, 1.15-1.88) at 12 months, declining to 1.27 (95% CI, 1.07-1.51) at trial end, with significant heterogeneity of the effect size by time (P = .02 for interaction). No such time-varying heterogeneity was observed with the sitagliptin effects on hHF in TECOS.

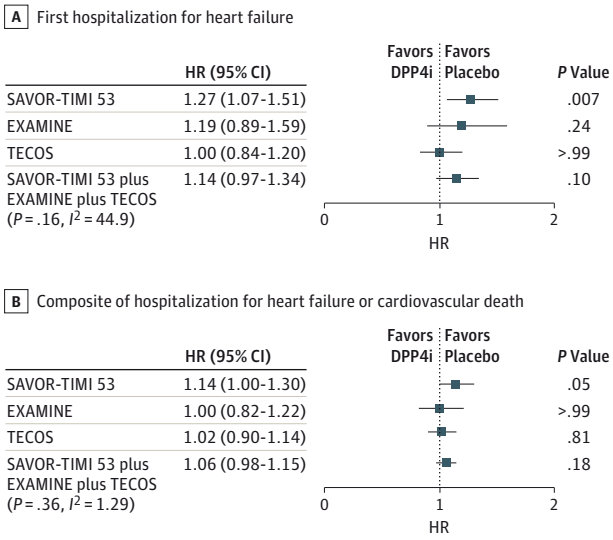
There was uniform prospective ascertainment and central adjudication of hHF throughout the TECOS using the same definition as the SAVOR-TIMI 53 and EXAMINE trials,[10,11] excluding another possible cause of the discordant hHF findings. While many of the hHF-related analyses in the SAVOR-TIMI 53 and EXAMINE trials were post hoc, each of the 3 trials identified hHF as a prespecified secondary analysis. Unexpected SAVOR-TIMI 53 and EXAMINE hHF findings reported during the conduct of TECOS led to the development of a formal HF statistical analysis plan before trial completion and unmasking. While this a priori planning yields some incremental statistical conservatism, our analysis methods largely parallel and extend those reported from the SAVOR-TIMI 53 and EXAMINE trials. Accordingly, statistical limitations are unlikely to account for the discordance in hHF findings.

To date, there has been no clear explanation as to the mechanisms by which some DPP4i agents might increase HF risk. It is possible that DPP4i pharmacological differences could account for the differential hHF risks, which was evident for example with the thiazolidinediones, for which a meta-analysis[6] demonstrated within-class qualitative differences for HF risk. Most important for the thiazolidinediones, other markers of HF are also affected, including higher rates of peripheral edema, weight gain, and increased circulating brain natriuretic peptide (BNP),[5,20] while no such associations have been reported for the DPP4i class. In the SAVOR-TIMI 53 trial, N-terminal pro-BNP increased slightly in both randomized groups, with a slightly greater mean increase in the placebo group compared with the saxagliptin group.[10] In the EXAMINE trial, BNP declined slightly in both randomized groups, with no difference between alogliptin and placebo.[11] Natriuretic peptide assessments are not presently available from TECOS. Sitagliptin use was not associated with increased weight in TECOS (eFigure 1D in the Supplement), with similar neutral weight effects of saxagliptin and alogliptin in the SAVOR-TIMI 53 and EXAMINE trials, respectively.[10,17] However, given the absence of adverse DPP4i effects on weight in these 3 trials and on natriuretic peptides in SAVOR-TIMI 53 and EXAMINE, the interpretation of these observations is limited.

It remains possible that the increased hHF observed in the SAVOR-TIMI 53 trial and the numerical imbalance in hHF found in the EXAMINE trial are due to chance, with analyses largely post hoc and not adjusted for multiplicity of comparisons or controlled for type I error. However, this possibility remains an unlikely explanation for the discordant observations between the trials. Despite the uncertain statistical validity inherent in post hoc analyses, the validity of the observation in the SAVOR-TIMI 53 trial is supported by the large number of hHF events (n = 517) (yielding robust statistical power), the prospective collection and adjudication of hHF events, and the time-dependent increase in hHF emerging soon after study drug initiation. This validity is supported, although not proved, by previously published meta-analyses[12,13] of data from these trials and others evaluating the effect of DPP4i agents on HF risk.

The present results have certain limitations. TECOS included patients with well-controlled glucose levels and excluded patients with severe kidney dysfunction. Therefore, the present observations may not apply to patients with such exclusion criteria. However, no increased risk was observed with sitagliptin use among those with baseline mild or moderate kidney impairment. Although designed to achieve balance in glycemic control between the groups, there was a mean 0.3% lower A_{1c} level in the sitagliptin group over the trial duration, which could confound the direct drug effects with the glycemic effects on the outcomes assessed. Limited clinical detail is available for the hHF events, with no imaging information available on cardiac structure and function, and other objective measures of HF, such as measurement of circulating natriuretic peptides, were not captured. The trial duration was longer than most trials assessing antihyperglycemic medications reported to date, with a follow-up period of up to 5 years, but the longer-term CV safety and efficacy of sitagliptin

Figure 3. Meta-Analysis of SAVOR-TIMI 53, EXAMINE, and TECOS



DPP4i indicates dipeptidyl peptidase 4 inhibitor; EXAMINE, Examination of Cardiovascular Outcomes With Alogliptin vs Standard of Care; HR, hazard ratio; SAVOR-TIMI 53, Saxagliptin Assessment of Vascular Outcomes Recorded in Patients With Diabetes Mellitus-Thrombolysis in Myocardial Infarction 53; and TECOS, Trial Evaluating Cardiovascular Outcomes With Sitagliptin.

cannot be assessed. Exploratory analyses planned in the supplemental HF statistical analysis plan were additional to those planned at the start of the trial and not analyzed under strict hierarchical statistical testing planned for key end points associated with hypotheses. Limitations of the meta-analysis include overall low hHF event rates (despite the large sample sizes of the trials), limited participation in each of the trials of patients with prior HF (13%-28% across the trials), and a short median follow-up duration for each of the trials (range, 1.5-3 years), precluding the ability to assess longer-term effects. In addition, although hHF events were prospectively captured and centrally adjudicated using similar processes and common definitions across each of the 3 trials, all of the hHF results reported derive from post hoc, exploratory analyses. Therefore, the findings should be interpreted carefully because these analyses were not adjusted for multiplicity.

Conclusions

The results of the present analyses demonstrate that sitagliptin use did not affect the risk for hHF or related adverse clinical outcomes, overall or across selected subgroups of interest. In the context of the primary findings from TECOS that demonstrated noninferiority of the effects of sitagliptin vs placebo on major atherosclerotic adverse CV events, the present results provide further support that sitagliptin may be safely used in a population of patients with T2DM at high CV risk.

ARTICLE INFORMATION

Accepted for Publication: January 22, 2016.

Published Online: April 13, 2016. doi:10.1001/jamacardio.2016.0103.

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Obtained funding: Koglin, Holman.
Administrative, technical, or material support: Standl, Green, Bethel.
Study supervision: Van de Werf, Armstrong, Cornel, Halvorsen, Ambrosio, Holman, Peterson.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr McGuire reported receiving personal fees from Boehringer Ingelheim, Janssen Research and Development LLC, Sanofi US Services Inc, Genentech Inc, Merck Sharp & Dohme Corp, Daiichi Sankyo Inc, Lilly USA, Novo Nordisk, GlaxoSmithKline, Takeda Pharmaceuticals North America, Bristol-Myers Squibb, AstraZeneca, Orexigen, Lexicon, Eisai, Regeneron, Janssen, Boehringer Ingelheim, Merck, Pfizer, and Genfit; reported receiving personal fees from the University of Oxford, Duke Clinical Research Institute, Partners Healthcare, and Cleveland Clinic Foundation; and reported receiving nonfinancial support from Gilead Sciences. Dr Van de Werf reported receiving personal fees from Merck. Dr Armstrong reported receiving grants, personal fees, and nonfinancial support from Merck and reported receiving grants from AstraZeneca. Dr Standl reported receiving personal fees from the Oxford Diabetes Trials Unit, AstraZeneca, Bayer, Boehringer Ingelheim, Merck Serono, EXCEMED, Novartis, and Sanofi. Dr Koglin reported being an employee of Merck Sharp & Dohme Corp, a subsidiary of Merck & Co, Inc. Dr Green reported receiving grants from Merck Sharp & Dohme Corp, AstraZeneca, and GlaxoSmithKline; reported receiving grants and personal fees from Merck Sharp & Dohme Corp; reported receiving other support from Boehringer Ingelheim; and reported receiving personal fees from Bioscientifica and the Endocrine Society. Dr Bethel reported receiving grants, personal fees, and other support from Merck Sharp & Dohme Corp; reported receiving other support from Boehringer Ingelheim, Novo Nordisk, and GlaxoSmithKline; and reported receiving nonfinancial support from Bayer. Dr Cornel reported receiving personal fees from Merck and Eli Lilly. Dr Lopes reported receiving consulting fees and research grants from Bristol-Myers Squibb; reported receiving research grants from GlaxoSmithKline; and reported receiving consulting fees from Boehringer Ingelheim, Bayer, and Pfizer. Dr Halvorsen reported receiving personal fees and other support from Merck Sharp & Dohme Corp and reported receiving personal fees from Pfizer, Bristol-Myers Squibb, Sanofi, Bayer, and AstraZeneca. Dr Ambrosio reported receiving personal fees from Menarini, Merck, Boehringer Ingelheim, and Angelini. Dr Buse reported received consulting fees from Eli Lilly, Hoffmann-La Roche, Bristol-Myers Squibb, Liposcience, GI Dynamics, Amylin, Orexigen, Elcylex, Merck, Novo Nordisk, Metavention, TransTech Pharma, PhaseBio, AstraZeneca, Dance Biopharm, Takeda, and Quest; reported receiving grants from Amylin, Novo Nordisk, Medtronic MiniMed, Eli Lilly, Tolerex, Osiris, Halozyme, Pfizer, Hoffmann-La Roche, Merck, Sanofi, Johnson & Johnson, Bristol-Myers Squibb, Andromeda, Boehringer Ingelheim, Orexigen, GlaxoSmithKline, Takeda, GI Dynamics, Astellas, AstraZeneca, MacroGenics, Intarcia Therapeutics, Lexicon, and Scion NeuroStim; reported having stock or stock options in PhaseBio; reported receiving personal fees and other support from Merck Sharp & Dohme Corp; and reported being a member of a variety of nonprofit boards (American Diabetes Association, DiabetesSisters, Taking Control of Your Diabetes, AstraZeneca Healthcare Foundation, Bristol-Myers Squibb Together on Diabetes Foundation, and the National Diabetes Education Program). Dr Josse reported receiving grants or personal fees from Merck, AstraZeneca, Janssen, and Eli Lilly. Dr Lachin reported receiving personal fees from Merck, Boehringer Ingelheim, Gilead Pharmaceuticals, Jansen Pharmaceuticals, Eli Lilly, Novartis, and GlaxoSmithKline. Dr Pencina reported receiving grants from Merck, AstraZeneca, and the Bristol-Myers Squibb Foundation and reported receiving personal fees from Theracos. Dr Lokhnygina reported receiving grants from Merck, Janssen Research & Development, AstraZeneca,

GlaxoSmithKline, and Bayer HealthCare AG. Dr Holman reported receiving grants and personal fees from Merck; reported receiving grants from Bayer, AstraZeneca, and Bristol-Myers Squibb; reported receiving personal fees from Amgen, Bayer, Intarcia, Novartis, Novo Nordisk, and Owen Mumford Ltd; and reported receiving other support from GlaxoSmithKline, Janssen, and Takeda. Dr Peterson reported receiving grants and personal fees from Janssen; reported receiving grants from Eli Lilly; and reported receiving personal fees from AstraZeneca, Bayer, and Sanofi. No other disclosures were reported.

Funding/Support: The Trial Evaluating Cardiovascular Outcomes With Sitagliptin (TECOS) was funded by Merck Sharp & Dohme Corp, a subsidiary of Merck & Co, Inc.

Role of the Funder/Sponsor: Merck Sharp & Dohme Corp had no role in the analyses of the data or in writing the first draft of the report. The authors are solely responsible for the design and conduct of the study; collection, management, analysis, and interpretation of the data; drafting and editing of the manuscript; and its final contents. Merck Sharp & Dohme Corp reviewed and commented on the final draft.

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Additional Contributions: We thank the patients, without whom this study and these analyses would not have been possible, and the following academic partners and contract research organizations for their assistance with the Trial Evaluating Cardiovascular Outcomes With Sitagliptin (TECOS): Parexel International, Jubilant Clinsys Limited, Clinogent, Canadian VIGOUR Centre, Green Lane Coordinating Centre, and South Australian Health and Medical Research Institute. Robert Califf served as joint chair of the TECOS until taking up the post of deputy commissioner of the US Food and Drug Administration on March 1, 2015.

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